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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/921,937	08/03/2001	Marc Feldmann	65019-DC-PCT-US/JPW/AJM/N	1212

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/921,937	FELDMANN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-69* is/are pending in the application.

4a) Of the above claim(s) *38-41,51-54 and 64-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-37,42-50 and 55-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election, filed 10/30/03, with traverse of Group I and the species of autoimmune disease and the specific disease or disorder of rheumatoid arthritis (claims 32-37, 42-50 and 55-69). The traversal is on the ground(s) that the Invention of the Groups I-VIII are not independent since they all relate to methods of treating TNF-mediated disease and the examination of the entire application would not constitute a burden to search.

This is not found persuasive because the inventions are distinct as noted in the previous Restriction Requirement, as shown by the distinctness described therein. Applicant is reminded that MPEP 803 states that the Inventions be either independent or distinct and a burden on the Examiner if restriction is required. Also, applicant's attention is directed to MPEP 806.05 for issues of distinctness.

Regarding applicant's comments about undue burden, the MPEP 803 states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search".

As pointed out previously, prior to setting forth the restriction requirement, it was pointed out that the claims are drawn to patentably distinct methods which rely upon TNFα antagonists that do not comprise a common structural feature that contributes to their common utility and, in turn, rely upon distinct products. The methods rely upon TNF-specific antibodies, p55TNFα receptors, p75TNFα receptors, pentoxifylline, rolipram, thalidomide, tenidap, A2b adenosine receptor agonist and a A2b adenosine receptor enhancer. These TNFα antagonists differ in structure and modes of action to such an extent and require non-coextensive searches to such an extent that they are considered separately patentable. The examiner notes that these molecules do not share a substantial structural feature essential to a common utility. Therefore, the restriction will be set forth for each of the various groups, irrespective of the format of the claims, because these are not proper species.

Applicant's arguments are not found persuasive because of the reasons of record.
The requirement is still deemed proper and is therefore made FINAL.

Claims 32-69 are pending.

Claims 32-37, 42-50 and 55-63 are under consideration as they read on the elected invention.

Claims 38-41, 51-54 and 64-69 have been withdrawn from consideration by the examiner 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species.

Claims 1-31 have been canceled previously.

2. Applicant's submission, filed 10/30/03, for Sequence Compliance based upon the previous compliance of parent application USSN 09/690,775 is acknowledged.

3. The filing date of the instant claims is deemed to be the filing date of parent application USSN 08/690,775, i.e. 8/1/96. Priority application USSN 08/403785 and PCT/GB94/00462 does not support the broader claims of the instant application, including "preventing a tumor necrosis factor-mediated disease", "tumor factor-mediated disease", "binds to one or more amino acids of hTNFα selected from the group consisting of about 87-108 and about 58-80", "cA2" and "epitope of cA2" . If applicant desires priority prior to 8/1/96; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

If applicant desires priority prior to 8/1/96; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

4. Applicant should amend the first line of the specification to update the status of the priority applications. USSN 08/690,775 is now U.S. Patent No. 6,270,766 .

5. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

The use of trademarks have been noted in this application. A TRADEMARK should be capitalized or accompanied by the ™ or ® symbol wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

6. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 45-46:

It is apparent that the cA2 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line / hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

Given the prosecution in parent application USSN 08/690,775 is now U.S. Patent No. 6,270,766, the the conditions for the deposit of biological materials under 35 USC 112, first paragraph, with respect to cA2 have been satisfied

8. Claim 32-34 and 37 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32-34 and 37 are indefinite in the recitation of "tumor necrosis factor-mediated disease" because the characteristics of said diseases are ill-defined and ambiguous. It is not clear whether said diseases reads on any inflammatory condition wherein TNF is present, wherein TNF has a direct role in pathology or wherein TNF has an indirect role in pathology. Although TNF contributes to certain conditions associated with inflammatory diseases, an artisan would not necessarily classify these diseases as TNF-mediated diseases, but rather inflammatory diseases wherein TNF plays some role. These claims are further ambiguous in the recitation of TNF since there are different members associated with TNF, and it is not clear whether any disease with any role played by any TNF falls into the metes and bounds of "TNF-mediated disease". Applicant should consider amending the claims to specific diseases or inflammatory diseases, where appropriate.

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 32-37, 42 and 55-63 are rejected under 35 U.S.C. § 102(e) as being anticipated by Mak et al. (U.S. Patent No. 6,190,691) (1449) (see entire document).

Mak et al. teach the use of TNF antagonists, including anti-TNF antibodies and fragments thereof (e.g. column 7, paragraph 3; column 9, paragraph 3; column 11, paragraph 3; column 42, paragraph 3) in combination with methotrexate (column 41, paragraph 2; Immunosuppressants; columns 59-61, including column 60, paragraph 1) in various dosages and schedules encompassed by the claimed methods (columns 53-56) to treat rheumatoid arthritis (e.g., see column 2, paragraph 1; column 3, lines 48-55; column 8, paragraphs 1 and 3; column 9, paragraphs 2-3; column 64, paragraph 1-2) (see entire document, Summary of the Invention, Detailed Description of the Invention). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations, including the epitope specificities and dosing schedules would be inherent properties of the referenced methods to treat rheumatoid arthritis with anti-TNF antibodies and methotrexate. Given the inhibitory properties of the referenced anti-TNF antibodies, the claimed functional properties and epitope specificities, including the cA2 competing antibodies would have been inherent properties of the referenced anti-TNF antibodies (e.g. column 7, paragraph 3; column 9, paragraph 3; column 11, paragraph 3; column 42, paragraph 3).

12. Claims 32-37, 42-50 and 55-63 are rejected under 35 U.S.C. § 103 as being unpatentable over Mak et al. (U.S. Patent No. 6,190,691) AND/OR Adair et al. (U.S. Patent No. 5,994,510) (1449) in view of the Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992; pages 1305-1312) and Aggarwal et al. (U.S. Patent No. 5,672,347) (1449).

Mak et al. teach the use of TNF antagonists, including anti-TNF antibodies (e.g. column 7, paragraph 3; column 9, paragraph 3; column 11, paragraph 3; column 42, paragraph 3) in combination with methotrexate (column 41, paragraph 2; Immunosuppressants; columns 59-61, including column 60, paragraph 1) in various dosages and schedules (columns 53-56) to treat rheumatoid arthritis (e.g., see column 2, paragraph 1; column 3, lines 48-55; column 8, paragraphs 1 and 3; column 9, paragraphs 2-3; column 64, paragraph 1-2) (see entire document, Summary of the Invention, Detailed Description of the Invention, including columns). Mak et al. differs from the claimed invention by not disclosing the well known use of recombinant antibodies.

Adair et al. teach the use of recombinant anti-TNF antibodies and fragments thereof to treat autoimmune diseases, including arthritis (see column 11, paragraph 8), alone or in combination with other active ingredients (column 11, paragraph 5), including well known methods of modes of administration (column 12)(see entire document). Adair et al. differs from the claimed methods by not disclosing the well known use of methotrexate in the treatment of arthritis

Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992) disclose the well known use of methotrexate in the treatment of rheumatoid arthritis; pages 1305-1312, particularly page 1311, Cytotoxic or Immunosuppressive Drugs).

Given the teachings of Mak et al., Adair et al. and the Merck Manual of Diagnosis and Therapy, one of ordinary skill in the art at the time the invention was made would have been motivated to select the combination of anti-TNF antibodies in combination with the immunosuppressant methotrexate to treat rheumatoid arthritis. Given the inhibitory properties of the referenced anti-TNF antibodies by Mak et al. and Adair et al., the claimed functional and epitope specificities, including the cA2 competing antibodies would have been expected or intrinsic properties of the referenced anti-TNF antibodies. Providing the claimed recombinant anti-TNF antibodies and fragments thereof encompassed by the instant claims (e.g. chimeric, humanized, resurfaced antibody) would have been obvious to the ordinary artisan to provide therapeutic antibodies in order to decrease the immunogenicity of therapeutic antibodies and to increase half-life of antibodies to achieve effective amounts of anti-TNF antibodies. The various therapeutic modalities are either explicitly taught by Mak et al. or would have been obvious to one of ordinary skill in the art to provide effective therapeutic amounts of immunosuppressive regimens in order to meet the needs of the patients, herein, patients with rheumatoid arthritis.

In addition to teaching the use of anti-TNF antibodies to treat various autoimmune diseases, Aggarwal et al. teach that the combination of TNF antagonists and anti-inflammatory agents provides for the use of these agents in lesser dosages when used alone. An ordinary artisan would have been motivated to provide anti-TNF antibodies to lessen the amount of methotrexate, given its know toxicities at the time the invention was made. It was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See MPEP 2144.06. Here, the prior art teaches combining antagonists encompassed by the claimed invention by teaching the use of anti-TNF antibodies and/or methotrexate to treat rheumatoid arthritis with other agents to inhibit the same disease. Here, too, the references teach the art known advantages of employing two immunosuppressives at the time same time, as evidenced by Aggarwal. et al.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention

13. Claims 45-46 are rejected under 35 U.S.C. § 103 as being unpatentable over Mak et al. (U.S. Patent No. 6,190,691)(1449) AND/OR Adair et al. (U.S. Patent No. 5,994,510) (1449) in view of the Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992; pages 1338 and 2435-2437)and Aggarwal et al. (U.S. patent No. 5,672,347) (1449),
as applied to claims 32-37, 42-50 and 55-63 above and further in view of Le et al. (U.S. Patent No. 5,919,452) (1449).

The above teachings did not disclose the particular anti-TNF cA2 specificity encompassed by claims.

Le et al. teach the use of chimeric anti-TNF antibodies, including the cA2 specificity (columns 10-20) to treat a number of TNF related pathologies (columns 33-35; Therapeutic Methods of Treating TNF-Related Pathologies), including known methods of administration to achieved the desired effect alone or in combination with other therapeutic agents (columns 35-38, Therapeutic Administration) (see entire document, including Detailed Description of the Invention and Claims)

Given the properties of the anti-TNF, particularly cA2-specific antibodies taught by Le et al., one of ordinary skill in the art would have been motivated to substitute or to apply this inhibitory cA2 anti-TNF antibody to treat rheumatoid arthritis as taught above. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention

14. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

a timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. a Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 32-37, 42-50 and 55-69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,270,766. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims anticipate the instant claimed methods.

16. Claims 32-37, 42-50 and 55-69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,270,766. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims anticipate the instant claimed methods.

17. Claims 32-37, 42-50 and 55-69 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims of copending application USSN 09/754,004. Although the conflicting claims are not identical, they are not patentably distinct from each other because the pending claims of the instant and copending applications are drawn to the same or nearly the same methods of treating tumor necrosis mediated diseases by administering methotrexate and a TNFα antagonist, including TNFα-specific antibodies, as the elected invention in each application.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
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